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Estimating risk for unexpected uterine leiomyosarcoma on the basis of uterine weight and age

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Summary

Purpose of investigation: The aim of the study was to estimate an incidence rate based on uterine weight and age for unexpected uterine leiomyosarcoma (ULMS) in patients with presumed uterine leiomyoma (UL) who had undergone total laparoscopic hysterectomy (TLH) or laparoscopic-assisted vaginal hysterectomy (LAVH) or laparoscopic supracervical hysterectomy (LSH) or laparoscopic myomectomy (LM). *Materials and Methods:* Patients aged 18-64 years who had diagnoses of presumed benign ULs and had undergone TLH or LAVH or LSH or LM between 2002 and 2013 (n = 21,600) from the ClinformaticsTM Data Mart Database were included in this study. Uterus size was identified by specific Current Procedural Terminology (CPT) codes from patients' medical claims and age were stratified into four groups: 18–34, 35-44, 45-54, and 50–64 years. *Results:* The overall incidence of unexpected ULMS was 1.39 cases per 1,000 (one in 720). The incidence was 1.14 per 1000 (one in 874) in the patients with uteri ≤ 250 grams, whereas it was 2.20 per 1000 (one in 454) in the patients with uteri > 250 grams. After age stratification, the rate was 1.31 cases per 1000 (one in 765) in 35-44 age group, 1.26 cases per 1000 (one in 792) in 45-54 age group, and 3.78 cases per 1000 (one in 265) in 55-64 age group. No unexpected ULMS was found in the patients aged 18-34 years. The patients aged 55-64 years were at a higher risk with an adjusted odds ratio of 3.41 [95% CI 1.22–9.52, $p = 0.03$] when comparing to patients aged 18-44 years. Uterine weight was marginal significantly ($p = 0.08$) associated with the incidence rate of unexpected ULMS after adjustments. *Conclusion:* In this dataset evaluation, the risk of unexpected ULMS was lower among the patients with uteri ≤ 250 grams when compared to those with uteri > 250 grams. In addition, age substantially influenced the incidence of unexpected ULMS. According to the findings obtained from the database, uterine weight and age would be useful triage parameters in estimating more accurate risk of encountering with unexpected ULMS. It also has potential to improve informed consent process.

Key Words: Uterine leiomyoma; Uterine leiomyosarcoma; Incidence; Hysterectomy; Laparoscopy.

Introduction

Uterine leiomyosarcomas (ULMSs), with an estimated incidence of one to two cases per 100,000 women, account for 42–60% of all uterine sarcomas [1-3]. Frequent symptoms of ULMS are quite similar to those reported by patients with uterine leiomyoma (UL) [2-5]. Imaging studies, such as computed tomography, magnetic resonance imaging, Doppler ultrasound, and serum lactate dehydrogenase have been examined to distinguish ULMS from UL, but none of them are individually sufficient or reliable for appropriate triage of patients in the preoperative period [6-10]. Since the endometrial biopsy fails to diagnose ULMS in a significant portion of patients as well, the definitive diagnosis frequently necessitates a final histopathologic review following surgery [11]. As a result, surgical specimens collected for the presumed diagnosis of UL can result in a diagnosis of ULMS [12, 13].

Recently, identifying the incidence rate of unexpected ULMS has been become a specific focus of interest due to increasing concerns about the postoperative outcomes of preoperatively undiagnosed ULMS. Therefore, many institutes have published their results to contribute to the existing literature, but their results vary significantly. Considering the fact that UL is the most common reason to perform a hysterectomy, and minimally invasive approaches have become the preferred method of UL management because of its favorable impact on patient quality of life, a substantial effort should be carried out to reach a better interpretation in estimating the incidence of unexpected ULMS [14, 15].

Previous studies generally have given incidence rates of unexpected ULMS without considering the uterine weight of their cohorts. The aim of this study was to use a US database to provide a contributory data to estimate the incidence of unexpected ULMS, based on uterine size in patients with presumed UL, who had undergone total laparoscopic hysterectomy (TLH) or laparoscopic-assisted vaginal hysterectomy (LAVH) or laparoscopic supracervical hysterectomy (LSH) or laparoscopic myomectomy (LM). Further, the difference in incidence was stratified by age in this study.

Materials and Methods

This retrospective cohort study was performed using 2002–2013 health insurance claims data from Clinformatics DataMart, which is a database consisting of geographically diverse, privately insured individuals in the US [16]. The database contains deiden-

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Table 1. — *Procedure codes based on ICD-9-CM and CPT.*

		CPT Codes
Total laparoscopic hysterectomy	Uterus ≤ 250 g	58570
	Uterus > 250 g	58572
Total laparoscopic hysterectomy with removal of tube(s) and/or ovary(ies)	Uterus ≤ 250 g	58571
	Uterus > 250 g	58573
Laparoscopic-assisted vaginal hysterectomy	Uterus ≤ 250 g	58550
	Uterus > 250 g	58553
Laparoscopic-assisted vaginal hysterectomy with removal of tube(s) and/or ovary(ies)	Uterus ≤ 250 g	58552
	Uterus > 250 g	58554
Laparoscopic supracervical hysterectomy	Uterus ≤ 250 g	58541
	Uterus > 250 g	58543
Laparoscopic supracervical hysterectomy with removal of tube(s) and/or ovary(ies)	Uterus ≤ 250 g	58542
	Uterus > 250 g	58544
Laparoscopic myomectomy	Uterus ≤ 250 g	58545
	Uterus > 250 g	58546

CPT—Current Procedural Terminology.

tified information on more than 45 million individuals who have at least one reported medical claim, approximately 80% of whom purchased health insurance through their employers. The database contains a higher percentage of white, young, middle-aged adults than is present in the overall US population and have been used in other published studies [17-19]. Since the data is deidentified, Institutional Review Board approval was not required for this study.

The study population included patients aged 18 to 64 years with primary diagnosis of UL and that had undergone total TLH or LAVH or LSH or LM from 2002 to 2013 (n = 42,865). Subjects were excluded if they did not have continuous insurance coverage one year before and after the operation (n=21,223) or had a diagnosis of ULMS in years before the surgeries were performed (n=42), resulting in 21,600 patients included in the final study cohort.

Diagnoses and procedures were identified based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and Current Procedural Terminology (CPT) codes from patients' medical claims. The ICD-9-CM codes that identify UL are 218, 218.0, 218.1, 218.2, 218.9, 219, 219.1, 219.8, and 219.9. For ULMS, the ICD-9-CM codes are 179 and 171.9. The procedure codes for total TLH or LAVH or LSH or LM used to create the present study population are shown in Table 1.

Age was determined by subtracting year of birth from year of surgical procedure. Study individuals were stratified into four age groups: 18–34, 35-44, 45-54, and 55–64 years. The geographic regions were categorized into four groups: Northeast, Midwest, South, and West based on information on member enrollment file. Year of surgical procedure (2002–2013) was included in the analyses. Medical claims were used to identify study outcome of ULMS within one year after the operation.

Descriptive statistics were used for sample characteristics. Unadjusted incidence of unexpected ULMS was calculated in both the total study population and the subpopulations stratified by age groups and uterine size. A multivariate logistic regression was used to test whether age and uterine size had a significant difference in the diagnosis of ULMS after the procedure, adjusting for type of surgery, geographic region, and year of procedure. SAS version 9.3 was used for statistical analyses.

Table 2. — *Characteristics of the study population.*

	Total		≤ 250 g		> 250 g	
	n	%	n	%	n	%
All	21600	100	16607	100	4993	100
Age (years)						
18 - 34	1305	6.04	1237	7.45	68	1.36
35 - 44	8408	38.92	6744	40.61	1664	33.32
45-54	10300	47.69	7325	44.11	2975	59.58
55-64	1587	7.35	1301	7.83	286	5.73
Region						
Northeast	1179	5.46	861	5.18	318	6.37
Midwest	4769	22.08	3661	22.04	1108	22.19
South	12601	58.34	9785	58.92	2816	56.40
West	3051	14.13	2300	13.85	751	15.04
Year						
2002	529	2.45	528	3.18	1	0.02
2003	709	3.28	611	3.68	98	1.96
2004	791	3.66	664	4.00	127	2.54
2005	808	3.74	661	3.98	147	2.94
2006	1011	4.68	802	4.83	209	4.19
2007	1476	6.83	1162	7.00	314	6.29
2008	1983	9.18	1515	9.12	468	9.37
2009	2309	10.69	1764	10.62	545	10.92
2010	2739	12.68	2051	12.35	688	13.78
2011	3006	13.92	2211	13.31	795	15.92
2012	3304	15.30	2466	14.85	838	16.78
2013	2935	13.59	2172	13.08	763	15.28
Type of surgery						
TLH	5884	27.24	4013	24.16	1871	37.47
LAVH	8938	41.38	6998	42.14	1940	38.85
LSH	4287	19.85	3105	18.70	1182	23.67
LM	2491	11.53	2491	15.00	0	0.00

Total laparoscopic hysterectomy: TLH,
Laparoscopic-assisted vaginal hysterectomy: LAVH,
Laparoscopic supracervical hysterectomy: LSH,
Laparoscopic myomectomy: LM.

Results

Table 2 presents characteristics of the study group. 38.9% (8,408 patients) of the study group was aged 35-44 years, 47.6% (10,300 patients) was aged 45-54 years, and 7.3% (1,587 patients) was aged 55-65 years. 76.8% (16,607 patients) of the study group had a uterus ≤ 250 grams. Geographic distribution revealed 58.3% of patients from the southern region of the United States. The number of cases steadily increased in the last ten years. Most of patients had LAVH (41.4%) or TLH (27.2%).

There were 30 cases with diagnosis of ULMS in the study population, 11 of whom were aged 35-44 years, 13 of whom were aged 45-54 years, and remaining six patients were aged 55-64 years. No unexpected ULMS was found in the patients aged 18-34 years. Table 3 represents the incidence rates based on uterine size and age brackets. The overall incidence of unexpected ULMS was 1.39 cases per 1,000 (one in 720). Based on uterine size, the incidence was 1.14 per 1000 (one in 874) in the patients with uteri ≤ 250

Table 3. — *Based on age brackets and uterine weight, the incidence of unexpected uterine leiomyosarcoma (ULMS) in one year after the operation (per 1,000) in patients who had undergone TLH or LAVH or LSH or LM for presumed uterine leiomyoma.*

		Total	≤ 250 g	> 250 g
All ages	1.39	1.14	2.20	
Age stratification	18 - 34	0.00	0.00	0.00
	35 - 44	1.31	1.18	1.82
	45 - 54	1.26	0.81	2.35
	55 - 64	3.78	3.84	3.49
Type of Surgery	TLH or LAVH	1.34	1.27	1.57
	LSH	1.63	0.64	4.23
	LM	1.20	1.20	N/A

N/A – not applicable.

Table 4. — *Multivariable logistic regression model.*

		OR	95% CI	*p*
Size (grams)	< 250	Ref	N/A	0.08
	> 250	2.00	0.92 - 4.35	
Age (years)	18-44	Ref	N/A	0.03
	45-54	1.03	0.44 - 2.37	
	55-64	3.41	1.22 - 9.52	
Type of surgery	TLH or LAVH	Ref	N/A	0.89
	LSH	1.21	0.51 - 2.90	
	LM	1.19	0.32 - 4.44	

The odds ratio estimate was adjusted for region and year of operation in a multivariable exact logistic regression model.
N/A – not applicable, Ref: reference
Total laparoscopic hysterectomy: TLH,
Laparoscopic-assisted vaginal hysterectomy: LAVH,
Laparoscopic supracervical hysterectomy: LSH,
Laparoscopic myomectomy: LM.

g, whereas it was 2.20 per 1,000 (one in 454) in the patients with uteri > 250 grams. Although this difference was not statistically significant, the incidence of unexpected ULMS was twice as high in the patients with uteri larger than 250 grams (Table 4). After age stratification, the rate was 1.31 cases per 1,000 (one in 765) in 35-44 age group, 1.26 cases per 1,000 (one in 792) in 45-54 age group, and 3.78 cases per 1,000 (one in 265) in 55-64 age group, irrespective of uterine weight. The patients aged 55 - 64 years were at a higher risk with an adjusted odds ratio of 3.41 [95% confidential interval (CI) 1.22–9.52, $p = 0.03$] when comparing to the patients aged 18-44 years old (Table 4). With regards to uterine weight, the difference in incidence rate of unexpected ULMS between uteri size ≤ 250 and > 250 grams was larger in patients aged 35-44 and 45-54 years than in patients aged 55 -64 years.

Although no significant effect of the type of surgery existed on the incidence of unexpected ULMS in the present study population, the patients with uteri larger than 250 grams who had undergone LSH had a higher risk of being diagnosed with unexpected ULMS (Table 3).

Discussion

Following the statement by FDA concerning about use of morcellation, utilizing minimally invasive surgery to perform a hysterectomy could be less feasible in patients with large uterus and UL, due to difficulties in removing specimen. However, smaller specimens can be easily extracted through vagina in most cases without requiring a morcellator. The database used for the present study showed that the overall incidence of unexpected ULMS was 1.39 in 1,000 (one in 720). Another group recently studied 6,360 hysterectomies performed for benign indications; irrespective of the route of surgery [20]. The incidence of unexpected uterine sarcoma was 2.7 in 1,000 when only UL was accepted as the indication of hysterectomy (the database used in the present study showed 1.39 in 1,000). The prsent authors found that the risk of unexpected ULMS was 1.31 cases per 1,000 (one in 765) in 35-44 age group and 1.26 cases per 1,000 (one in 792) in 45-54 age group, which increased to 3.78 cases per 1,000 (one in 265) in 55-64 age group. A study showed that the incidence was 2.2 in 1,000 for women younger than 55 years and 8.0 in 1,000 for women 55 years or older when the only indication of UL was included [25]. In contrast to the present study, their results included all types of uterine sarcoma, but similar to this study, the risk of being diagnosed with uterine sarcoma after the surgery was clearly influenced by the age factor. Brohl *et al.* assessed a total of 10,120 patients by combining their results with previous studies and generated the risk of all uterine sarcomas as 2.94 cases per 1,000 (one in 340) and the risk of ULMS alone as 1.78 cases per 1,000 (one in 562) [12, 13, 21-27] after myomectomy and hysterectomy cases, regardless of surgical techniques used [21]. Moreover, they found a directly proportional relationship between age and the risk of unexpected uterine sarcoma: 4.6 in 1,000 (one in 216) in the 50–54 age group, 6.3 in 1,000 (one in 158) in the 55–59 age group, and 6.4 in 1,000 (one in 157) in the 60–64 age group [25]. The estimated risk was higher in women older than 44 years when compared with the overall risk of one in 340 in their study.

In support of the uterine weight correlation, Graebe *et al.* [28] assessed 1,361 hysterectomies performed with minimally invasive surgery for benign conditions. The incidence of unexpected ULMS was 2.2 in 1,000 in their series. In this single center pathology data, all uterine neoplasia, including epithelial cancers, revealed that the mean uterine weight of the cases with a diagnosis of malignancy was 293.5 grams, which was statistically higher when compared to those with a diagnosis of benign (117.5 grams). Lieng *et al.* [29] created an algorithm model to screen each case based on patients' ages, imaging, uterus sizes, and endometrial biopsies. They found 26 primary cases diagnosed with ULMS after reviewing a total of 4,791 cases of women

who underwent open or laparoscopic procedures for presumed ULs. Six of these cases were diagnosed preoperatively by endometrial sampling, and the remaining 20 cases were diagnosed postoperatively. The risk of unexpected ULMS was 4.1 in 1,000. However, the authors emphasized that 14 of the 20 operations were performed assuming they had a diagnosis of ULMS based on large tumor size with irregularity on imaging and postmenopausal status. In the study by Picerno *et al.* [30], the mean of uterine weight in final histopathologic review was 840.0 grams in group with uterine malignancy and 217.7 grams in group with non-malignancy ($p = 0.028$). Their findings also suggested that women who had surgery for UL were at a higher risk of being diagnosed with unexpected uterine malignancy compared to those who had surgery for other benign indications. The present study support the studies conducted by Graebe *et al.*, Lieng *et al.*, and Picerno *et al.* Since uterine weight may play an incidence changer role in diagnosing unexpected ULMS on final pathology, existing literature may need to be interpreted for the data regarding incidence of unexpected ULMS according to stratification of uterine weight. While the overall risk of unexpected ULMS was one in 562 in combinations of previous studies [21], the overall risk was lower in the present study, with one in 720 [21]. Moreover, the patients with presumed UL and uteri ≤ 250 grams received less often a diagnosis of ULMS (one in 874) after a laparoscopic procedure, even much less in patients aged 18 – 54 years according to the database used for the present study (one in 1,093).

American College of Obstetricians and Gynecologists (ACOG) reported the risk of unexpected stromal sarcoma and ULMS after gynecologic surgery as one in 500 [31]. On the initial US Food and Drug Administration (FDA) evaluation, the risk of unexpected uterine sarcomas and ULMS was calculated based on one in 352 and one in 458, respectively, among patients who underwent hysterectomy or myomectomy for presumed UL [32]. Age brackets were not used in the FDA review because no adequate data likely existed in the studies evaluated. The present authors took into consideration both age and uterine size in their calculation, and provided the risk assessment for age groups and uterine size. The overall incidence of unexpected ULMS was lower with a rate of one in 720 in the present study population compared to the rate of one in 485 calculated by the FDA. This difference might have been originated as some studies evaluated by FDA included cases performed abdominally.

Based on the database used for the present analysis, 74.2% of the patients who had undergone TLH or LAVH had uteri ≤ 250 gramd. The present authors speculate that the majority of uteri ≤ 250 grams can be extracted through vagina without dividing the uterine tissue into smaller pieces or fragments in hysterectomy practice. For this reason, the risk of spreading sarcoma into intra-abdominal organs may be lower in comparison to those with uteri > 250 grams or those who need to undergo LSH or LM. Given these reasons, uterine weight and type of surgical procedure may be significant parameters in evaluating the risk of upgrading ULMS after the surgery. A guideline that shows likelihood of extractability of uterus from vagina would at least be helpful to minimize the risk of cancer spread in a significant proportion of patients.

The present study has some limitations. First, the findings are only applicable to those with private insurance and not those covered by public insurance or no insurance. Second, claims data are subjected to coding errors; a diagnosis code for UL or ULMS on a medical claim may not be an accurate proof of those diseases. Third, patients can only be followed up when they have continual insurance coverage. Fourth, the authors did not include morcellation used to remove the specimen due to lack of specific procedures available in claim data. In addition, to maintain the homogeneity of study population across years, the authors did not include patients received robot-assisted procedures. The FDA approved robotic-assisted hysterectomies in 2005 and did not have specific codes available until 2008. Robotic surgery was also a relative new technology at that time. Selection bias by surgeon might have been played a role in management of patients. Last, information related to social economic status, race/ethnicity, and body weight, which may influence risk of ULMS could not be obtained in claim data. This study, however, has strengths. First, using large claims databases acquired from the general population to study rare diseases, such as ULMS, allow for estimation of real-world treatment patterns. Second, large claims databases evaluate a large, geographically diverse population with complete episodes of care across different healthcare settings. Last, the databases provide longitudinal tracking at the patient level.

Conclusion

The present study showed to have a lower risk of unexpected ULMS in women with uteri < 250 grams who had a laparoscopic surgery due to presumed UL. This risk was a much lower in women younger than 55 years. Since diagnostic workups are known to be insufficient in detecting presence of ULMS preoperatively, these findings would assist us in placing an effort to interpret the data, revealing the incidence of unexpected ULMS. Uterine weight and age would be useful parameters in the triage of patients who need to undergone a minimally invasive procedure.

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